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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/021,121	12/06/2001	Ingrid W. Caras	GENENT.046DV1	3508

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EXAMINER	
NICHOLS, CHRISTOPHER J	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/021,121	CARAS, INGRID W.	
	Examiner	Art Unit	
	Christopher J Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35 and 40-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35 and 40-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Preliminary Amendment filed 2 April 2002 has been received and entered in full.

2. The Preliminary Amendment filed 6 December 2001 has been received and entered in full.

3. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher Nichols.

Specification

4. The disclosure is objected to because of the following informalities: misspelling "half-life i approximately" (pp. 27 line 19); outdated address for ATCC, Applicant is advised the current address for ATCC is: American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209 (pp. 34 line 2). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims **35** and **40-46** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

6. The claims are drawn very broadly to a method for accelerating neovascularization of any kind of wound comprising applying an angiogenically effective amount of AL-2 polypeptides which share 85% or greater sequence homology to the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 4.

7. The specification teaches that AL-2 is an Eph-related tyrosine kinase ligand.

8. However, the specification fails to provide any guidance for the successful treatment of any wounds with AL-2 polypeptides which share 85% or greater sequence homology to the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 4. And since resolution of the various complications in regards to targeting the effect of a neurotrophic factor an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations AL-2 polypeptides which share 85% or greater sequence homology to the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 4 followed by administration to wounds to evaluate signs and symptoms to correlate with neovascularization. In the absence of any guidance from the specification and in view of the variants, homologues, analogues, orthologues, fragments, muteins, isoforms which are encompassed by AL-2 polypeptides which share 85% or greater sequence homology to the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 4 the amount of experimentation would be undue. Further, the claims as instantly presented

constitute an invitation to experiment and one would have been unable to practice the invention over the scope claimed.

9. Additionally, a person skilled in the art would recognize that predicting the efficacy of using variants, homologues, analogues, orthologues, fragments, muteins, isoforms which are encompassed by AL-2 polypeptides which share 85% or greater sequence homology to the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 4 based solely on suggestion and sequence homology as highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed therapeutic method, such a disclosure would not be considered enabling since the state of angiogenesis is highly unpredictable. The factors listed below have been considered in the analysis of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

10. The following references are cited herein to illustrate the state of the art of angiogenesis.

11. On the breadth of the claims, WO 97/36919 (9 October 1997) Cerretti teaches that Eph family receptor ligands are a diverse group of proteins that affect the growth, differentiation, and survival of cells. Tissue distribution of the Eph receptors is diverse and the Eph receptor ligands have been found to bind to more than one receptor of the Eph receptor family (pp. 1). Therefore

the skilled artisan is not apprised of what the effect of administration of AL-2 would be, nor which receptors it would interact with, what signaling pathways it would trigger or suppress, or what the effect, in any, AL-2 would have on neovascularization.

12. On the nature of the invention, in regards to the variants, homologues, analogues, orthologues, fragments, muteins, isoforms which are encompassed by AL-2 polypeptides which share 85% or greater sequence homology to the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 4, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 433-506]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the

nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art

which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

13. On the nature of the invention, Díaz-Flores *et al.* (October 1994) "Angiogenesis: an update." Histology and Histopathology **9(4)**: 807-843 teach that angiogenesis involves the complex process of neovascularization which includes the following events: a) endothelial cell (EC) and pericyte activation; b) basal lamina degradation; c) migration and proliferation of EC and pericytes; d) formation of a new capillary vessel lumen; e) appearance of pericytes around the new capillaries; f) development of a new basal lamina; g) capillary loop formation; h) persistence or involution, and differentiation of the new vessels; and i) capillary network formation and, eventually, organization into larger microvessels (pp. 807-819). Díaz-Flores *et al.* also teaches that the use of numerous "*in vivo*" and "*in vitro*" systems facilitate the assessment of angiogenesis control, in which angiogenic and antiangiogenic candidate substances may be tested. However, no such evidence is present in the Specification or the prior art to support the claims. And in light of the complexity of the claims goals, the skilled artisan is not reasonably instructed as to which, if any, rate determining steps of neovascularization variants, homologues, analogues, orthologues, fragments, muteins, isoforms which are encompassed by AL-2 polypeptides which share 85% or greater sequence homology to the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 4 are involved in to a degree which is considered effective. Also, no evidence is present that any one or all of the variants, homologues, analogues, orthologues, fragments, muteins, isoforms which are encompassed by AL-2 polypeptides which

share 85% or greater sequence homology to the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 4 will have any effect on neovasularization thus presenting an invitation to experiment. Firstly, to determine which steps any or all of the variants, homologues, analogues, orthologues, fragments, muteins, isoforms which are encompassed by AL-2 polypeptides which share 85% or greater sequence homology to the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 4 are involved in and then which of the multitude of variants, homologues, analogues, orthologues, fragments, muteins, isoforms which are encompassed by AL-2 polypeptides which share 85% or greater sequence homology to the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 4 have a desired effect.

14. On the level of predictability in the art, WO 97/15667 (1 May 1997) Davis *et al.*(**IDS**) teaches that the Eph-related transmembrane tyrosine kinases comprise the largest known family of receptor-like tyrosine kinases, with many members displaying specific expression in the developing and adult nervous system. The known members of the Eph family appear to be expressed exclusively in the nervous system (pp. 4). Therefore the skilled artisan is not provided guidance as to where the target of AL-2(a ligand of an Eph-related receptor) is expressed, what the effect of administration of AL-2 would be, nor which Eph-related transmembrane tyrosine kinase receptor it would interact with, or what the effect, in any, AL-2 would have on neovascularization.

15. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *prophetic suggestion* to the acceleration of the *neovascularization of wounds* as exemplified in the references herein.

16. Claims **35** and **40-46** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

17. The claims are drawn to polypeptides having at least 85% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claims are drawn to a genus of polypeptides that is defined by sequence identity.

18. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a partial structure in the form of a recitation of percent identity. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. The only adequately described species is a polypeptide comprising SEQ ID NO: 2 and 4. No active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus.

19. *Vas-Cath Inc. v. Mahurkar,* 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

20. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

21. Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 2 and 4, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

Summary

22. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on **(571) 272-0887**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Elizabeth C. Kemmerer

CJN
May 24, 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER

ELIZABETH KEMMERER
PRIMARY EXAMINER